a color scanner. Most preferably, the scanner is a standard color scanner of the type used to scan documents into computers. Such scanners are inexpensive and readily available commercially. For instance, an Epson Expression 636 (600 x 600 dpi), a UMAX Astra 1200 (300 x 300 dpi), or a Microtec 1600 (1600 x 1600 dpi) can be used. The scanner is linked to a computer loaded with software for processing the images obtained by scanning the substrate. The software can be standard software which is readily available commercially, such as Adobe Photoshop 5.2 and Corel Photopaint 8.0. Using the software to calculate greyscale measurements provides a means of quantitating the results of the assays. The software can also provide a color number for colored spots and can generate images (*e.g.*, printouts) of the scans which can be reviewed to provide a qualitative determination of the presence of a nucleic acid, the quantity of a nucleic acid, or both. In addition, it has been found that the sensitivity of assays such as that described in Example 5 can be increased by subtracting the color that represents a negative result (red in Example 5) from the color that represents a positive result (blue in Example 5). The computer can be a standard personal computer which is readily available commercially. Thus, the use of a standard scanner linked to a standard computer loaded with standard software can provide a convenient, easy, inexpensive means of detecting and quantitating nucleic acids when the assays are performed on substrates. The scans can also be stored in the computer to maintain a record of the results for further reference or use. Of course, more sophisticated instruments and software can be used, if desired.

A nanoparticle-oligonucleotide conjugate which may be used in an assay for any nucleic acid is illustrated in Figures 17D-E. This "universal probe" has oligonucleotides of a single sequence attached to it. These oligonucleotides can hybridize with a binding oligonucleotide which has a sequence comprising at least two portions. The first portion is complementary to at least a portion of the sequence of the oligonucleotides on the nanoparticles. The second portion is complementary to a portion of the sequence of the nucleic acid to be detected. A plurality of binding oligonucleotides having the same first portion and different second portions can be used, in which case the "universal probe", after hybridization to the binding oligonucleotides, can bind to multiple portions of the nucleic acid to be detected or to different nucleic acid targets.

In a number of other embodiments of the invention, the detectable change is created by labeling the oligonucleotides, the nanoparticles, or both with molecules (*e.g.*, fluorescent molecules and dyes) that produce detectable changes upon hydridization of the oligonucleotides on the nanoparticles with the target nucleic acid. For instance, oligonucleotides attached to metal and semiconductor nanoparticles can have a fluorescent molecule attached to the end not attached to the nanoparticles. Metal and semiconductor nanoparticles are known fluorescence quenchers, with the magnitude of the quenching effect depending on the distance between the nanoparticles and the fluorescent molecule. In the unhybridized state, the oligonucleotides attached to the nanoparticles interact with the nanoparticles, so that significant quenching will be observed. See Figure 20A. Upon hybridization to a target nucleic acid, the fluorescent molecule will become spaced away from the nanoparticles, diminishing quenching of the fluorescence. See Figure 20A. Longer oligonucleotides should give rise to larger changes in fluorescence, at least until the fluorescent groups are moved far enough away from the nanoparticle surfaces so that an increase in the change is no longer observed. Useful lengths of the oligonucleotides can be determined empirically. Metallic and semiconductor nanoparticles having fluorescent-labeled oligonucleotides attached thereto can be used in any of the assay formats described above, including those performed in solution or on substrates.

Methods of labeling oligonucleotides with fluorescent molecules and measuring fluorescence are well known in the art. Suitable fluorescent molecules are also well known in the art and include the fluoresceins, rhodamines and Texas Red. The oligonucleotides will be attached to the nanoparticles as described above.

In yet another embodiment, two types of fluorescent-labeled oligonucleotides attached to two different particles can be used. Suitable particles include polymeric particles (such as polystyrene particles, polyvinyl particles, acrylate and methacrylate particles), glass particles, latex particles, Sepharose beads and others like particles well known in the art. Methods of attaching oligonucleotides to such particles are well known in the art. See Chrisey et al., *Nucleic Acids Research*, **24**, 3031-3039 (1996) (glass) and Charreyre et al.,

Langmuir, **13**, 3103-3110 (1997), Fahy et al., *Nucleic Acids Research*, **21**, 1819-1826 (1993), Elaissari et al., *J. Colloid Interface Sci.*, **202**, 251-260 (1998), Kolarova et al., *Biotechniques*, **20**, 196-198 (1996) and Wolf et al., *Nucleic Acids Research*, **15**, 2911-2926 (1987) (polymer/latex). In particular, a wide variety of functional groups are available on the particles or can be incorporated into such particles. Functional groups include carboxylic acids, aldehydes, amino groups, cyano groups, ethylene groups, hydroxyl groups, mercapto groups, and the like. Nanoparticles, including metallic and semiconductor nanoparticles, can also be used.

The two fluorophores are designated **d** and **a** for donor and acceptor. A variety of fluorescent molecules useful in such combinations are well known in the art and are available from, *e.g.*, Molecular Probes. An attractive combination is fluorescein as the donor and Texas Red as acceptor. The two types of nanoparticle-oligonucleotide conjugates with **d** and **a** attached are mixed with the target nucleic acid, and fluorescence measured in a fluorimeter. The mixture will be excited with light of the wavelength that excites **d**, and the mixture will be monitored for fluorescence from **a**. Upon hybridization, **d** and **a** will be brought in proximity (see Figure 20B). In the case of non-metallic, non-semiconductor particles, hybridization will be shown by a shift in fluorescence from that for **d** to that for **a** or by the appearance of fluorescence for **a** in addition to that for **d**. In the absence of hybridization, the flurophores will be too far apart for energy transfer to be significant, and only the fluorescence of **d** will be observed. In the case of metallic and semiconductor nanoparticles, lack of hybridization will be shown by a lack of fluorescence due to **d** or **a** because of quenching (see above). Hybridization will be shown by an increase in fluorescence due to **a**.

As will be appreciated, the above described particles and nanoparticles having oligonucleotides labeled with acceptor and donor fluorescent molecules attached can be used in the assay formats described above, including those performed in solution and on substrates. For solution formats, the oligonucleotide sequences are preferably chosen so that